(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 November 2002 (14.11.2002)

PCT

(10) International Publication Number
WO 02/089835 A2

(51) International Patent Classification[7]: A61K 38/55, 9/20, A61P 31/12, 31/18

(21) International Application Number: PCT/EP02/04711

(22) International Filing Date: 29 April 2002 (29.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/288,410 3 May 2001 (03.05.2001) US

(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacharstrasse, CH-4070 Basel (CH).

(72) Inventors: INFELD, Martin, Howard; 6 Tuers Place, Upper Montclair, NJ 07043 (US). PHUAPRADIT, Wantanee; 42 Robinson Terrace, Clifton, NJ 07013 (US). SHAH, Navnit, Hargovindas; 203 Beverly Hill Road, Clifton, NJ 07012 (US). ZHANG, Lin; 900 Davidson Road, Apartment 56, Piscataway, NJ 08854 (US).

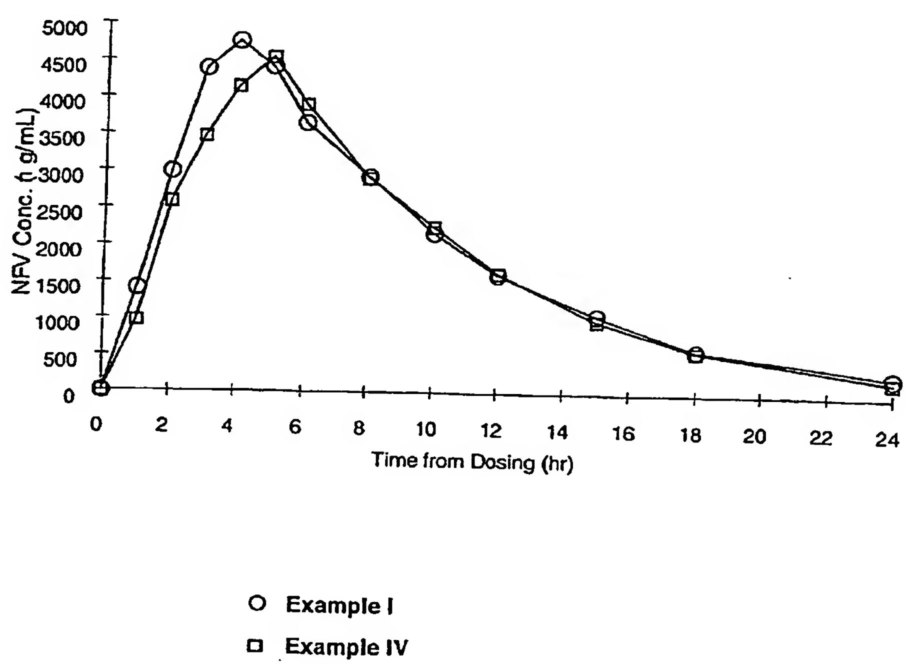
(74) Agent: RAUBER, Beat; 124 Grenzacherstrasse, CH-4070 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: PHARMACEUTICAL DOSAGE FORM OF AMORPHOUS NELFINAVIR MESYLATE



(57) Abstract: A solid unit oral pharmaceutical dosage form of amorphous nelfinavir mesylate is provided comprising amorphous nelfinavir mesylate, and a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, said copolymer having a melting point of at least 40°C. A hot melt granulation process for making the dosage form is provided.

WO 02/089835 A2

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Pharmaceutical Dosage Form of Amorphous Nelfinavir Mesylate

Nelfinavir mesylate is one of several protease inhibitors used to limit viral replication and improve immune function in HIV-infected individuals. Information regarding nelfinavir mesylate is reported in "Viracept (Nelfinavir Mesylate, AG1343): A Potent, Orally Bioavailable Inhibitor of HIV-1 Protease", Kaldor et al., J. Med. Chem., 40, 3979-85 (1997), and its use in the treatment of HIV is reported in "Nelfinavir: An Update on its Use in HIV Infection", Bardsley-Elliot et al., Drugs, 59(3), 581-620 (2000).

Nelfinavir mesylate is a white to off-white amorphous powder that is slightly soluble in water at pH less than or equal to 4. Nelfinavir mesylate has a molecular weight of 663.90 (567.79 as the free base).

Nelfinavir mesylate is commercially available as a 250 mg tablet (as nelfinavir free base). It is sold under the name Viracept® by Agouron Pharmaceuticals, Inc., a Pfizer company. Viracept® tablets are known to additionally contain calcium silicate, crospovidone, magnesium stearate, FD&C blue #2 powder, hydroxypropyl methylcellulose and triacetin. U.S. Patent No. 6,001,851 to Albizati et al., assigned to Agouron Pharmaceuticals, Inc., reports a tablet composition (formulation 9) containing 292 mg of an HIV inhibitor which can be nelfinavir mesylate. The patent does not specify the market formulation, Viracept®, although the reported composition contains calcium silicate, crospovidone and magnesium stearate. Calcium silicate and crospovidone each constitute 25% of the composition reported in the patent.

For adult patients, the recommended oral dosage of nelfinavir mesylate (calculated as nelfinavir free base) is 750 mg (3 x 250 mg tablets) 3 times daily or an alternative regimen of 1250 mg (5 x 250 mg tablets) twice daily. Whether a two- or three-times per day dosage program is followed, the tablet burden remains significant over the course of a day. Patient compliance is therefore a real concern.

Block copolymers of ethylene oxide and propylene oxide that are listed as poloxamers in the NF Monograph "Poloxamer" are available in a wide range of molecular weights and melting points. They are marketed under the name Lutrol® or Pluronic® by BASF Corporation. Poloxamers have been extensively used as pharmaceutical wetting and solubilizing agents, typically in small amounts.

It has also been noted that poloxamers can be used in pharmaceutical formulations to enhance the bioavailability of a drug. U.S. Patent No. 5,834,472 to Sangekar et al., for example, reports that including a non-ionic surfactant that is a block copolymer of ethylene oxide and propylene oxide in a composition of an antifungal compound having extremely low water solubility can enhance the bioavailability of the compound. U.S. Patent No. 5,281,420 to Kelm et al. addresses formulation of the drug tebufelone, an anti-inflammatory, analgesic and/or antipyretic agent that is essentially water-insoluble. Absorption of tebufelone is quite low from the gastrointestinal tract. Kelm et al. report a solid dispersion of tebufelone, produced by melting together poloxamer and tebufelone (melting point of 70°C) to form a homogeneous melt mixture. Solid dispersions of the homogeneous melt mixture result from cooling the mixture and allowing it to solidify. The poloxamer surfactant is included to provide the necessary solubilization of the highly insoluble drug in forming the melt mixture.

A high dosage strength solid unit oral dosage form, e.g., a tablet, of nelfinavir mesylate having satisfactory dissolution and bioavailability has apparently not been successfully developed prior to the present invention. This may be due in part to the hydrophobic nature of the drug, which accounts for its low aqueous solubility. In addition, nelfinavir mesylate in high dose solid unit dosage forms gels upon exposure to physiological fluid. The gel retards dissolution and bioavailability of the drug. The problem of gelling worsens with increased drug loading.

SUMMARY OF THE INVENTION

The present invention provides a solid unit oral pharmaceutical dosage form of amorphous nelfinavir mesylate comprising amorphous nelfinavir mesylate and a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, the copolymer having a melting point of at least 40°C. The high dose nelfinavir mesylate pharmaceutical dosage form of the invention exhibits satisfactory dissolution and bioavailability.

The present invention also provides a process for preparing a solid unit oral pharmaceutical dosage form of amorphous nelfinavir mesylate, comprising: (a) heating a blend of amorphous nelfinavir mesylate and a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, the copolymer having a melting point of at least 40°C at a temperature of from the melting point temperature of the copolymer to below the decomposition temperature of nelfinavir mesylate, (b) mixing the blend to form a melt granulation, and (c) processing the melt granulation into the solid unit oral dosage form of amorphous nelfinavir mesylate.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 presents dissolution profiles of 625 mg tablets of nelfinavir mesylate (Examples II and III) compared to that of the 250 mg market (tablet) formulation (Example I).

Figure 2 presents dissolution profiles of 625 mg nelfinavir mesylate tablets in accordance with the invention (Examples IV and V) compared to other 625 mg nelfinavir mesylate tablets (Examples II and III).

Figure 3 shows the effect of Poloxamer 188 concentration on the dissolution profiles of 625 mg tablets of nelfinavir mesylate (Examples VI, VII, VIII and IX).

Figure 4 shows mean plasma concentration versus time profiles after administration of 2 x 625 mg nelfinavir mesylate tablets of the invention (Example IV) compared to administration of 5 x 250 mg tablets of the market formulation (Example I).

DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that when amorphous nelfinavir mesylate is melt granulated with a pharmaceutically acceptable, water-soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide in accordance with the invention, a significant improvement in the dissolution rate of the drug is shown with resulting satisfactory bioavailability. The nelfinavir mesylate used for the solid unit dosage form of the invention is amorphous. Dosage amounts are calculated as nelfinavir free base, unless specified otherwise. The pharmaceutical dosage form of the invention is a high per unit dosage of the nelfinavir mesylate as compared to the 250 mg market formulation, and is amenable to oral administration. For patient compliance and acceptability, the maximum weight of a

solid unit oral pharmaceutical dosage form is typically from 1.0 g to 1.5 g. The present invention encompasses solid unit oral dosage forms having the nelfinavir mesylate in a dose from 400 mg, the dose at which the gelling potential of the nelfinavir mesylate begins to be problematic when formulated using conventional pharmaceutical excipients and processes, to 700 mg. The dosage form comprises nelfinavir mesylate in an amount of from 400 mg to 700 mg, preferably from 500mg to 700 mg. A preferable dosage amount is, for example, 625 mg.

The pharmaceutically acceptable, water-soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide in accordance with the present invention as a rule has a molecular weight of from 6,000 D to 18,000 D, preferably from 6800 D to 17500 D and a melting point of preferably 40°C to 60°C, more preferably from 49°C to 57°C. The hydrophil/lipophil balance ("HLB") value at 25°C expediently is at least 14, preferably 14 to 29, more preferably 22 to 29. The copolymer is readily water soluble. Typically, the copolymer of the present invention has an ethylene oxide content (percentage of oxyethylene-groups) of at least 70% by weight, preferably 70% to 85% by weight. Suitable pharmaceutically acceptable water-soluble, non-ionic synthetic block copolymers of ethylene oxide and propylene oxide are listed in the NF Monograph "Poloxamer". Preferred copolymers in accordance with the invention include Lutrol® or Pluronic® F68, F87, F108 and F127 (BASF Corporation). Very good results have been achieved with Pluronic® F68. The coplymers have the following characteristics:

Lutrol®	Poloxamer, NF	% Weight Oxyethylene	Molecular Weight (D)	Melting Point (°C)	HLB Value at 25°C
F68	188	81.8 ± 1.9	7680-9510	52	29
F87	237	72.4 ± 1.9	6840-8830	49	24
F108	338	83.1 ± 1.7	12700-17400	57	27
F127	407	73.2 ± 1.7	9840-14600	56	22

The pharmaceutical dosage form of the invention expediently contains the block copolymer in an amount of from 40% to 65% by weight of the nelfinavir mesylate, preferably from 45% to 60%, and more preferably from 50% to 55% by weight of the nelfinavir mesylate.

The nelfinavir mesylate dosage form of the present invention is advantageously produced by a hot melt granulation process. The hot melt granulation process of the present invention comprises blending the nelfinavir mesylate and the copolymer, and heating the blend to a temperature of from the copolymer melting point temperature to below the decomposition temperature of nelfinavir mesylate. The hot melt granulation process results in a melt granulation which comprises granules of the drug embedded in the copolymer. The heated blend is mixed until such melt granules are obtained. Preferably, the blend is heated to a temperature at which the nelfinavir mesylate remains in solid form in the nelfinavir mesylate-copolymer mixture. A jacketed mixer or a hot melt extruder can be used to prepare a melt granulation.

One or more excipients can be included in the mixture of nelfinavir mesylate and copolymer. The excipient can be selected from the group of stabilizers, wetting agents, binders, disintegrants, diluents and solubilizers. Examples of additives for inclusion in the nelfinavir mesylate-copolymer mixture are povidone, polyethylene glycol, and polyoxyethylene sorbitan esters of C_8-C_{18} fatty acids, (e.g., Tween® 20, Tween® 60, and Tween® 80), etc. The heated blend is mixed

and melt granules are formed, thus resulting in a melt granulation that includes one or more pharmaceutically acceptable excipients. The melt granulation can then be milled and mixed with one or more pharmaceutical excipients. The excipient added to the milled granulation can be selected from the group of lubricants, disintegrants and diluents. The pharmaceutical excipient may be, for example, microcrystalline cellulose, corn starch, magnesium stearate, etc.

The hot melt granulation process of the present invention comprises hot melt granulating the nelfinavir with a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, the copolymer having a melting point of at least 40°C , at a temperature of from the melting point temperature of the copolymer to below the decomposition temperature of nelfinavir mesylate. Preferably, the temperature is from 50ºC to 85ºC, with the proviso that the temperature be at least at the melting point temperature of the copolymer. The melt granulation, prepared with or without any additional pharmaceutical excipients, is then processed into a solid unit oral dosage form.

For preparing tablets, the melt granulation can be processed into a solid unit oral dosage form by milling, lubricating, compressing (tabletting), and, typically, aqueous film coating.

In an embodiment of the present invention, tablets are prepared as follows:

a) blend amorphous nelfinavir mesylate in an amount of from 400 mg to 700 mg (calculated as free base) per unit dosage with the copolymer of the invention in an amount from 40% to 65% by weight of the nelfinavir mesylate;

b) mix the powder blend from step (a) in a jacketed high shear granulator at 60°±10°C with the proviso that the temperature be at least at

the melting point temperature of the copolymer, or in a jacketed hot melt extruder at 80°±5°C, until melt granules are obtained;

cool the melt granulation to room temperature;

c) mill the granulation from step (b) into a fine powder;

d) blend the milled granulation from step (c) with other suitable tablet diluents, such as corn starch and microcrystalline cellulose;

e) lubricate the granulation from step (d) with a suitable lubricant, such as magnesium stearate;

f) compress the final blend from step (e) on a tablet press;

g) aqueous film coat the tablet from step (f).

A pharmaceutical dosage form of the invention, can alternatively be prepared by hot melt extrusion. Hot melt extrusion can be used to make molded tablets.

The solid oral unit dosage form can be a tablet, capsule or caplet. The pharmaceutical composition can include one or more pharmaceutically acceptable excipients selected from the group of stabilizers, wetting agents, binders, disintegrants, diluents, solubilizers and lubricants. For example, the excipient can be microcrystalline cellulose, corn starch, magnesium stearate, povidone, polyethylene glycol, and polyoxyethylene sorbitan esters of C_8-C_{18} fatty acids (e.g., Tween® 20, Tween® 60 and Tween® 80), etc.

EXAMPLES

Example I: 250 mg Nelfinavir Mesylate Tablet (Market Formulation)

Commercial Viracept® tablets were used in the present Example.

Example II: 625 mg Nelfinavir Mesylate Tablet

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Crospovidone	240.000
Calcium Silicate	217.375
Purified Water	q.s.**
Magnesium Stearate	12.000
Tablet Weight	1200.000

* Equivalent to 625 mg of Nelfinavir free base
** Removed during processing

The tablet formulation of Example II was produced by a conventional aqueous wet granulation process.

Example III: 625 mg Nelfinavir Mesylate Tablet

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Crospovidone	100.000
Dibasic Calcium Phosphate, Anhydrous	169.375
Purified Water	q.s.**
Magnesium Stearate	10.000
Tablet Weight	1010.000

* Equivalent to 625 mg of Nelfinavir free base
** Removed during processing

The tablet formulation of Example III was produced by a conventional aqueous wet granulation process.

Example IV: 625 mg Nelfinavir Mesylate Tablet of the Invention

Composition	mg/tablet
Kernel:	
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	394.375**
Corn Starch	60.000
Magnesium Stearate	7.000
Kernel Weight	1192.000
Film Coat:	
HPMC 2910 – 6 cps	7.341
Pharmacoat 603	10.500
Talcum	5.969
Titanium Dioxide	5.682
Red Iron Oxide	0.048
Yellow Iron Oxide	0.048
Aquacoat ECD-30	5.987***
Triacetin	2.425
Purified Water	138.030****
Total Weight	1230.000

* Equivalent to 625 mg of Nelfinavir free base
** Approximately 54% w/w of Nelfinavir Mesylate
*** Based on dry basis-solids content of a 30% suspension
**** Removed during processing; this amount of water does not include the amount of water present in Aquacoat ECD-30

The tablet formulation of Example IV was produced using a hot melt granulation process, as follows:

Step 1) Nelfinavir mesylate and Lutrol® F68 were mixed in a jacketed high shear granulator with a temperature setting at 25°±5°C for 5 minutes using impeller at low speed and chopper at low speed.

Step 2) The jacketed temperature was raised to 60°±10°C with the proviso that the temperature was at least at the melting point temperature of the Lutrol® F68, while mixing of the powder blend (step 1) in the high shear granulator was continued using impeller at low speed and chopper at low speed until a suitable granulation was obtained, at which time the impeller and chopper were turned off.

Step 3) The heat to the jacket was turned off. The product was cooled to room temperature by passing tap water (25°±5°C) into the jacketed vessel, with intermittent jogging of both impeller and chopper at low speed.

Step 4) The granulation from step 3 was passed through a mill.

Step 5) Approximately 50% of the milled granulation from Step 4 was placed into a twin shell blender. Corn starch and magnesium stearate (passed through a #30 mesh stainless steel screen) were added into the blender. The remainder of the milled granulation from step 4 was added to the blender and mixed for 8 minutes.

Step 6) The granulation from step 5 was compressed into a tablet containing nelfinavir mesylate, 625 mg (as free base).

Step 7) The coating suspension was prepared as follows: In a stainless steel container, triacetin and Aquacoat ECD-30 were dispersed in purified water using a propeller mixer, mixing for 45 minutes. HPMC 2910-6 cps, Pharmacoat 603, talcum, titanium dioxide, yellow iron oxide and red iron oxide were added and

slowly dispersed, while mixing gently to avoid air entrapment. Mixing was continued for another 60 minutes or until a uniform suspension was obtained.

Step 8) The kernels from step 6 were placed into a perforated coating pan. They were heated with warm inlet air of 50°±3°C with intermittent jogging until the outlet air temperature reached 38°±3°C.

Step 9) The inlet air temperature was increased to 60°±3°C. The kernels from step 8 were sprayed with the coating suspension from step 7, stirred continuously, using an air spray system and maintaining the outlet air temperature at 38°±3°C. The film coat, 38 mg per tablet, was applied (range 35-41 mg on a dry basis).

Step 10) The inlet air temperature was reduced to 40°±3°C and the coated tablets were dried by jogging until the loss on drying of the tablets at 90°C was less than 1.8%. The heat was turned off and the tablets were cooled to room temperature by occasional jogging.

<u>Example V: 625 mg Nelfinavir Mesylate Tablet of the Invention</u>

Composition	mg/tablet
Kernel:	
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	394.375**
Microcrystalline Cellulose	40.000
Corn Starch	20.000
Magnesium Stearate	7.000
Kernel Weight	1192.000
Film Coat:	
HPMC 2910 – 6 cps	13.140
Talcum	4.085
Titanium Dioxide	4.084

FD&C Blue #2	0.591
Aquacoat ECD-30	4.400***
Triacetin	1.700
Purified Water	117.290****
Total Weight	1220.000

* Equivalent to 625 mg of Nelfinavir free base
** Approximately 54% w/w of Nelfinavir Mesylate
*** Based on dry basis-solids content of a 30% suspension
**** Removed during processing; this amount of water does not include the amount of water present in Aquacoat ECD-30

The melt granulation method set forth in Example IV was used with the composition amounts set forth in the table above for the present example. Differences in the tablet coating are reflected in the following steps numbered 7 and 9 that here replace steps 7 and 9 of Example IV.

The coating suspension was prepared as follows: In a stainless steel container, triacetin and Aquacoat ECD-30 were dispersed in purified water using a propeller mixer, mixing for 45 minutes. HPMC 2910-6 cps, talcum, titanium dioxide and FD&C Blue #2 were added and slowly dispersed, while mixing gently to avoid air entrapment. Mixing was continued for another 60 minutes or until a uniform suspension was obtained.

The inlet air temperature was increased to 60°±3°C. The kernels from step 8 were sprayed with the coating suspension from step 7, then stirred continuously, using an air spray system and maintaining the outlet air temperature at 38°±3°C. The film coat, 28 mg per tablet, was applied (range 25-31 mg on a dry basis).

Example VI: 625 mg Nelfinavir Mesylate Tablet

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	182.656**
Corn Starch	102.616
Magnesium Stearate	10.262
Tablet Weight	1026.159

* Equivalent to 625 mg of Nelfinavir free base
** Approximately 25% w/w of Nelfinavir Mesylate

The tablet formulation of Example VI was produced by hot melt granulation, as follows:

Nelfinavir mesylate and Lutrol® F68 were blended in a mixer for 10 minutes.

The powder mixture from step 1 was added to a jacketed hot melt extruder set at 80º±5ºC while thorough mixing was continued until a uniform melt mixture was obtained.

Steps 3 to 6 under Example IV were then followed as steps 3 to 6 of the present example.

Example VII: 625 mg Nelfinavir Mesylate Tablet

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	243.542**
Corn Starch	109.457
Magnesium Stearate	10.946
Tablet Weight	1094.570

* Equivalent to 625 mg of Nelfinavir free base

** Approximately 33% w/w of Nelfinavir Mesylate

The same hot melt granulation procedure was followed as described in Example VI.

Example VIII: 625 mg Nelfinavir Mesylate Tablet of the Invention

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	343.824**
Corn Starch	120.725
Magnesium Stearate	12.073
Tablet Weight	1207.247

* Equivalent to 625 mg of Nelfinavir free base

** Approximately 47% w/w of Nelfinavir Mesylate

The same hot melt granulation procedure was followed as described in Example VI.

Example IX: 625 mg Nelfinavir Mesylate Tablet of the Invention

Composition	mg/tablet
Nelfinavir Mesylate	730.625*
Poloxamer 188 (Lutrol® F68)	443.215**
Corn Starch	131.892
Magnesium Stearate	13.189
Tablet Weight	1318.921

* Equivalent to 625 mg of Nelfinavir free base
** Approximately 61% w/w of Nelfinavir Mesylate

The same hot melt granulation procedure was followed as described in Example VI.

Example X: Dissolution Testing

Tablet formulations containing nelfinavir mesylate (Examples I-IX) were evaluated for dissolution in 900 mL of 0.1N hydrochloric acid solution equilibrated at 37°±0.5°C using a paddle method (USP Apparatus 2) at 50 rpm. Sample aliquots were taken at different time intervals and analyzed by UV spectrophotometry.

Figure 1 presents dissolution profiles of 625 mg tablet formulations of nelfinavir mesylate which do not contain the block copolymer of the present invention (Examples II and III) compared to that of the 250 mg market (tablet) formulation (Example I). The dissolution profiles of 625 mg nelfinavir mesylate tablets without block copolymer (Examples II and III) were significantly slower and less complete than that of the 250 mg market (tablet) formulation (Example I). The tablet formulations of Examples II and III contain conventional excipients and were produced by a conventional aqueous wet granulation process.

As shown in Figure 2, the results of the dissolution evaluation indicate that the dissolution profiles of 625 mg nelfinavir mesylate tablets in accordance with the invention (Examples IV and V) were significantly faster and essentially complete compared to the dissolution profiles of the 625 mg nelfinavir mesylate tablets which were prepared using conventional pharmaceutical excipients and a conventional aqueous wet granulation process (Examples II and III).

The dissolution profiles of tablets of Examples VI through IX are shown in Figure 3. The results indicate that the concentration of block copolymer plays a significant role with respect to the rate and completeness of dissolution of nelfinavir mesylate. Examples VI and VII contain Poloxamer 188 in an amount of 25% and 33% by weight of nelfinavir mesylate, respectively. Examples VIII and IX, which contain Poloxamer 188 in an amount of 47%, and 61% by weight of nelfinavir mesylate, respectively, show faster and more complete release.

Example XI: Pharmacokinetic Testing

Nelfinavir mesylate 250 mg tablets of the market formulation (Example I) and nelfinavir mesylate 625 mg tablets of the invention (Example IV) were evaluated for bioavailability in man. Each subject was administered a number of tablets of the given formulation totaling 1250 mg of nelfinavir mesylate (calculated as free base). In this study, 13 blood samples were drawn for each pharmacokinetic profile, i.e. at pre-dose, and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 24 hours after administration of the drug. Venous blood samples of approximately 5 ml were collected into heparinized tubes. Plasma was separated by centrifugation at 1500 g and 4°C for 10 minutes, within 60 minutes of drawing the blood. Plasma samples were subsequently stored at -20°C until analysis. Nelfinavir content in the plasma samples was determined by liquid chromatography – tandem mass spectrometry (LC-MS/MS). The limit of quantification was set to 4 ng/ml.

The plasma concentration versus time profiles were used for the estimation of pharmacokinetic parameters. Standard non-compartmental methods were applied using the software WinNonlin 3.1. The pre-dose sampling time of a profile was set to zero and the post-dose sampling times were used as actual times. The following parameters were estimated:

C_{max}, maximum observed plasma concentration

t_{max}, time of maximum observed plasma concentration

$AUC_{0\text{-}24h}$, calculated using WinNonlin computational rules for partial AUCs and the linear trapezoidal rule

$AUC_{0\text{-}inf}$, calculated by AUC_{last} + $(C_{last})/k)$, where an assessment of k (terminal elimination rate constant) was feasible

$t_{1/2}$, terminal half-life, calculated by Ln (2) / k, where an assessment of k was feasible

The results of this bioavailability evaluation are given in Table I below.

Table I: Summary of pharmacokinetic parameters after administration of 1250 mg of nelfinavir mesylate (as free base)*: 2 x 625 mg tablets of the invention (Example IV) compared to 5 x 250 mg tablets of the market formulation (Example I)

Parameter (Unit)	Nelfinavir 1250 mg (based on the free base)	
	Example I	Example IV
	N = 12	N = 12
AUC_{0-24}(x 10^3 hr ng/mL)		
Median (Min - Max)	43.5 (21.1 - 89.7)	37.0 (27.5 - 73.2)
Mean	44.4	42.3
Geometric Mean	41.8	40.0
CV%	38.6	37.4
C_{max} (ng/mL)		
Median (Min - Max)	5275 (2520 - 9590)	4585 (3680 - 8450)
Mean	5248	5200
Geometric Mean	4971	5042
CV%	34.9	27.7
t_{max} (hr)		
Median (Min - Max)	4.0 (3.0 - 6.0)	4.0 (2.0 - 6.0)
Mean	4.1	4.0
CV%	26.5%	35.4%
AUC_{0-inf} (x 10^3 hr ng/mL)		
Median (Min - Max)	45.3 (21.7 - 98.2)	37.8 (28.5 - 77.7)
Mean	46.5	43.7
Geometric Mean	43.5	41.1
CV%	41.2%	39.7%
$t_{1/2}$ (hr)		
Median (Min - Max)	4.4 (3.3 - 6.8)	3.9 (3.0 - 5.7)
Mean	4.5	3.9
Harmonic Mean	4.3	3.8
CV%	24.9%	22.0%

*With food

The data reported in Table I and plotted in Figure 4 indicate that the bioavailability in man of 2 x 625 mg nelfinavir mesylate tablets of the invention (Example IV) was comparable to that of 5 x 250 mg tablets of the market formulation (Example I) when administered with food. The present invention advantageously provides high dosage solid unit oral pharmaceutical compositions of nelfinavir mesylate having satisfactory dissolution and bioavailability.

Claims

1. A solid unit oral pharmaceutical dosage form of amorphous nelfinavir mesylate comprising amorphous nelfinavir mesylate , and a pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, said copolymer having a melting point of at least 40°C.

2. The dosage form according to claim 1, wherein said copolymer is present from 40% to 65% by weight of the nelfinavir mesylate.

3. The dosage form according to claims 1 or 2, wherein said copolymer has a melting point of 40°C to 60°C.

4. The dosage form according to claims 1 to 3, wherein said copolymer has a HLB value at 25°C of at least 14 .

5. The dosage form according to claim 4, wherein said copolymer has a HLB value at 25°C of 14 to 29 .

6. The dosage form according to claims 1 to 5, wherein said copolymer has an ethylene oxide content of at least 70 % by weight.

7. The dosage form according to claims 1 to 6, having a content of nelfinavir mesylate, calculated as nelfinavir base of 400 mg to 700 mg.

8. The dosage form according to claims 1 to 7, further comprising a pharmaceutically acceptable excipient selected from the group consisting of stabilizers, wetting agents, binders, disintegrants, diluents, solubilizers, and lubricants.

9. The dosage form according to claims 1 to 8, which is a tablet, a capsule or a caplet.

10. A process for making a solid unit oral pharmaceutical dosage form according to claims 1 to 9, comprising the steps of:

(a) heating a blend comprising amorphous nelfinavir mesylate and the pharmaceutically acceptable, water soluble, non-ionic synthetic block copolymer of ethylene oxide and propylene oxide, said copolymer having a melting point of at least 40°C, at a temperature of from the melting point temperature of the copolymer to below the decomposition temperature of nelfinavir mesylate,

(b) mixing the blend to form a melt granulation, and

(c) processing the melt granulation into said dosage form of amorphous nelfinavir mesylate.

11. Solid unit oral pharmaceutical dosage form according to claims 1 to 9 for use in therapy.

12. Solid unit oral pharmaceutical dosage form according to claim 10 for use in the treatment of HIV mediated diseases.

***

FIGURE 1

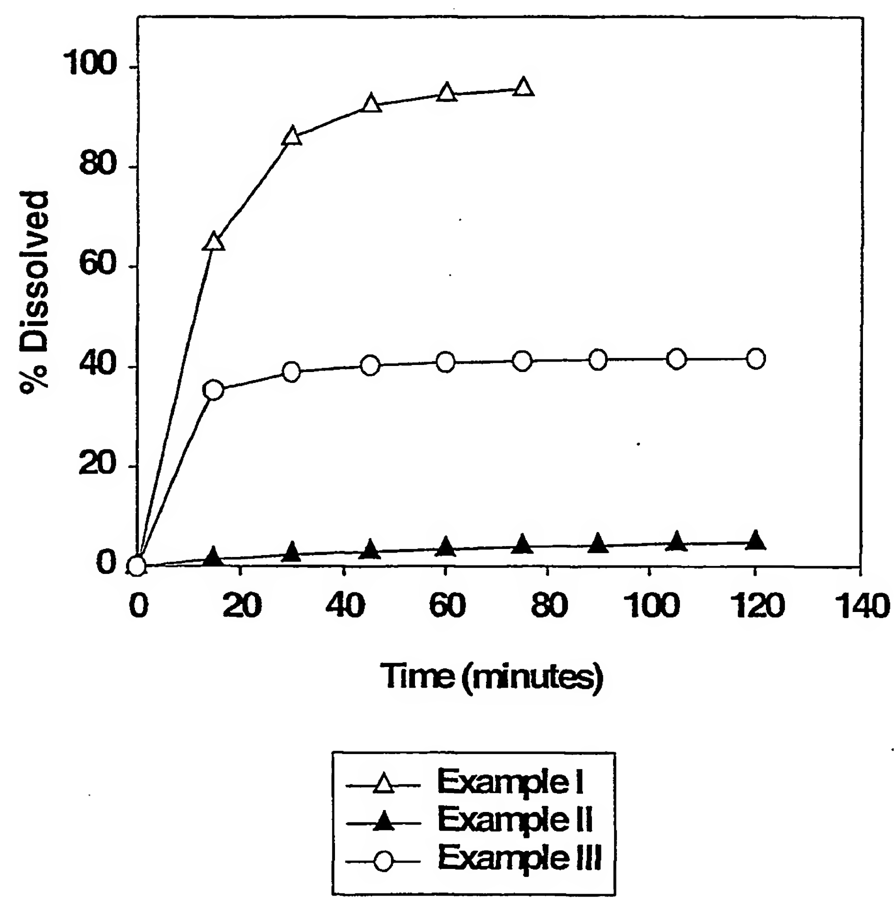

100
80
60
40
20
0
% Dissolved
0
20
40
60
80
100
120
140
Time (minutes)
Example I
Example II
Example III

FIGURE 2

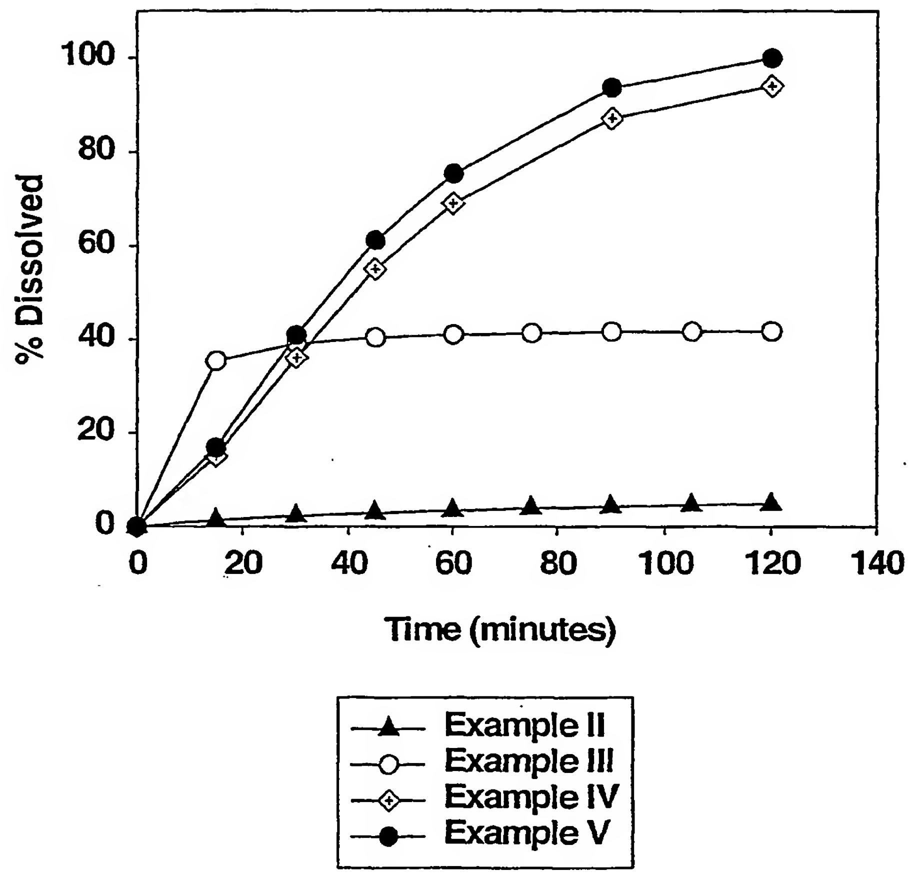

% Dissolved
0
20
40
60
80
100
0
20
40
60
80
100
120
140
Time (minutes)
Example II
Example III
Example IV
Example V

FIGURE 3

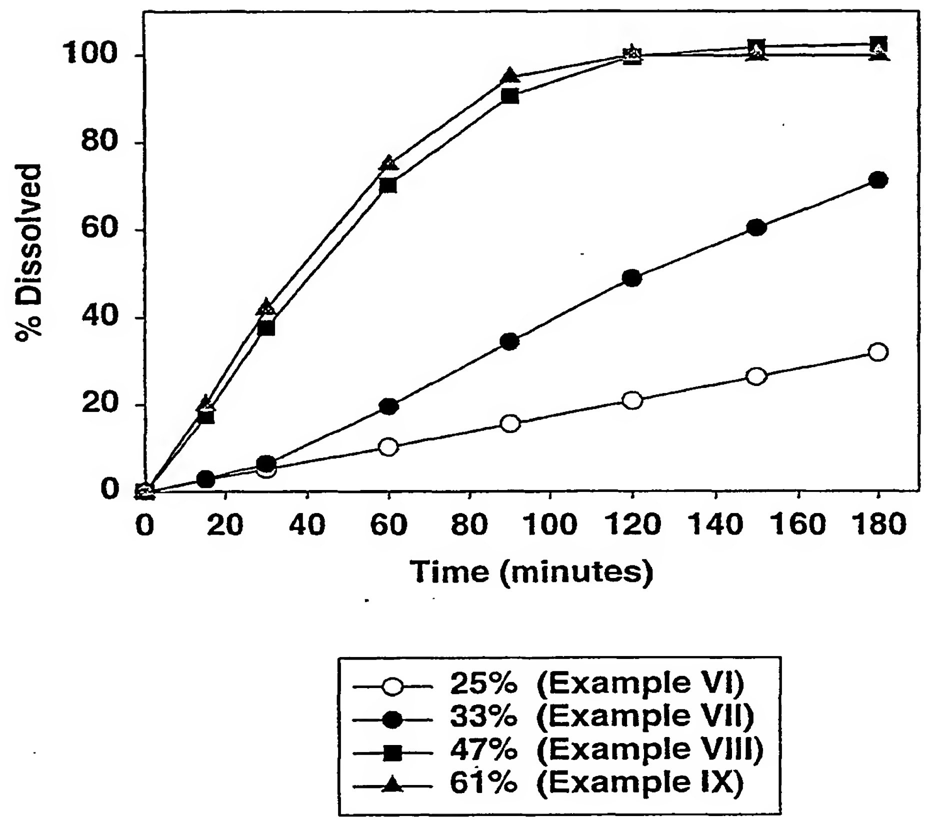
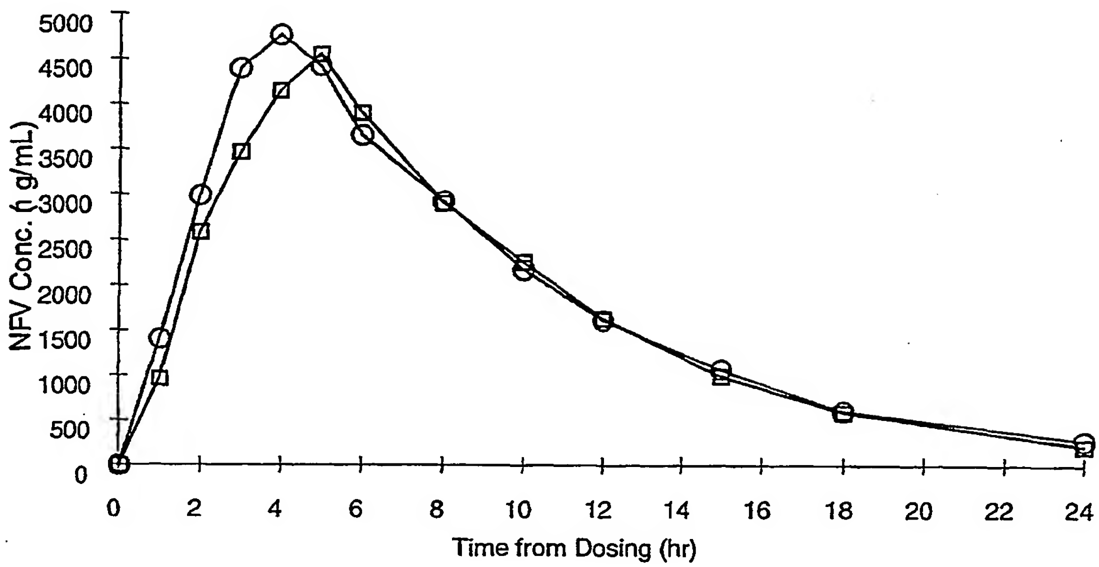

% Dissolved
0
20
40
60
80
100
0
20
40
60
80
100
120
140
160
180
Time (minutes)
25% (Example VI)
33% (Example VII)
47% (Example VIII)
61% (Example IX)

FIGURE 4



○ Example I

□ Example IV